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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,189	10/30/2001	Alan G. Harris	AL01182Q	9438

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,189	HARRIS ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006 and 28 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,12-15 and 52-62* is/are pending in the application.

4a) Of the above claim(s) *51-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,12-15 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, with traverse, with the atherosclerosis as the elected species is acknowledged. Claims 10, 12-15and 52 read on the elected species.

Claims 53-62 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

Status of Application

2. By Amendment filed 07/28/06, claims 1, 3-7, 18, 20-25, 28 and 30-35 have been cancelled; claim 1 has been amended; and claims 52-62 have been newly added.

3. Claims 10, 12-15 and 52 are currently pending for prosecution on the merits of the case.

Summary of Action

4. The rejection of claims 10, 12-15 and 52 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record.

5. The rejection of claims 1, 3-7, 10, 12-15, 18, 20-25, 28, 30-33 and 35 under 35 U.S.C. 102(b) as being anticipated by Aberg et al. (US 5731319) is not maintained in light of the amendment filed 07/28/06.

6. The rejection of claims 1, 3-7, 10, 12-15, 18, 20-25, 28, 30-33 and 35 under 35 U.S.C. 103(a) as being unpatentable over Aberg et al. (US 5731319) in view of Buckland et al. (EP 0968715 A1), and further in view of Gray (US 5627183), Kreutner et al. (US 5869479) and the applicant's admitted prior art of the record (page 2, lines 4-7 (Hospes, et al., Am. J. Epidemiol.,

Vol. 150. (No. 5), pp. 482-491, 1999)) is not maintained in light of the amendment filed 07/28/06.

7. The rejection of claims 1, 3-7, 10, 12-15, 18, 20-25, 28, 30-33 and 35 under the judicially created doctrine of double patenting over claims 1-4 of U. S. Patent No. 6114346 or claims 1-3 of U. S. Patent No. 6265414 and claims 1-13 of U. S. Patent No. 6432972 is not maintained in light of the amendment filed 07/28/06.

8. Applicant's amendment requiring "characterized by platelet activating factor activity and/or superoxide generation", "which is not suffering from allergic and/or inflammatory condition of the skin or upper airway passages", "to reduce the risk or prevent the occurrence of said cardiovascular disease" in claim 1 and "atherosclerosis" in claim 52 necessitates a new ground of rejection in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 10, 12-15 and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment introduces new negative limitation into the claimed invention, namely "which is not suffering from an allergic and/or inflammatory condition of the skin or upper

airway passages". The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly amended claims fail to find support in the original specification.

The specification discloses that immunologic responses to allergic and/or inflammatory conditions are involved in pathogenesis of cardiovascular disease (page 1, line 15 thru page 2, line 7 and page 3, lines 9-10) and the administration of desloratadine provide therapeutic utility in treating and/or reducing the risk of cardiovascular disease in a human suffering from an allergic and/or inflammatory condition (page 1, lines 2-5; page 3, lines 18-22; page 4, line 5 thru page 5, line 15; page 7, line 13 thru page 8, line 2). As the specific embodiment of the invention, the specification provides assays (in vitro) and demonstrates the activity of desloratadine in attenuating chemotaxis, adhesion and superoxide generation in eosinophils isolated from the blood of patients with allergic rhinitis or from those with allergic asthma (Example).

Therefore, it would have been clear to one skilled in the art, reading the instant disclosure, that the intended treatment group must have coextensive condition of said cardiovascular disease and allergic and/or inflammatory condition of the skin or upper airway passages, not excluding "allergic and/or inflammatory condition of the skin or upper airway passages".

As discussed above, the specification only positively states about the boundaries of the claim. There is no express statement about the negative limitation that can be found in the specification. Thus, the exclusion of said elements implies the inclusion of all other elements not expressly excluded, clearly illustrating that such negative limitations do, in fact, introduce new matter. The negative limitation recited in the present claims, which did not appear in the

specification filed, introduces new concepts and violate the description requirement of the first paragraph of 35 USC 112.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 10, 12-15 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific cardiovascular disease, for example atherosclerosis, angina pectoris and stroke, with the administration of desloratadine, does not reasonably provide enablement for "treating and/or preventing a cardiovascular disease characterized by platelet activating factor activity and/or superoxide generation". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The American Heritage Dictionary (Second College Edition, 1982) defines the term "prevent" as "anticipate or counter in advance, to keep from happening". The interpretation of the instant claims allows for the complete cure and eradication or total elimination of said cardiovascular diseases by the administration of said desloratadine.

The art recognizes that eosinophil infiltration is involved in a great measure in atopic dermatitis, allergic rhinitis, other allergic diseases and parasitic diseases; and demonstrates that the inhibition of eosinophil infiltration or chemotaxis is effective in treating bronchial asthma, chronic eosinophilic pneumonia, allergic rhinitis, allergic sinusitis, allergic conjunctivitis, eosinophilic gastroenteritis, atopic dermatitis, urticaria and parasitic infections (US 5922712; US 5837713; US 5891884; WO 94/06429). Furthermore, the art recognizes that administration of H1 receptor antagonist such as desloratadine and certrizine is effective in treating allergic and/or inflammatory condition of the skin or upper airway passages including rhinitis, asthma, urticaria or dermatitis (US 5698558; US 5731319; US 5869479; US 6103735), and demonstrate the positive correlation that H1 receptor antagonist, namely certrizine, is effective in inhibiting eosinophil chemotaxis (US 5698558; WO 94/06429; US 6258816).

However, it is not known that eosinophil infiltration is definite cause of cardiovascular diseases. Furthermore, the art does not recognize that the administration of said H1 receptor antagonist, desloratadine, or similar compounds would be effective in treating or preventing all types of cardiovascular diseases.

With respect to "prevention of cardiovascular diseases", the art recognizes the treatment of the specific cardiovascular diseases (e.g., stroke, shock, myocardial infarction, artheriosclerosis) but not their cure. The true fact of the state of the art is illustrated succinctly in

the "NIH Heart Disease & Stroke Research: Fact Sheet" (American Heart Association, 2004); "Cardiovascular Disease: Treatment for Stroke", Stanford Hospital & Clinics, 2003. Thus, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" or completely cure or eradication effect.

The relative skill of those in the pharmaceutical art is high. The unpredictability of the pharmaceutical art is very high. As stated above, applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The claims are very broad. Webster's New World Medical Dictionary (2nd Edition, 2003) defines a cardiovascular disease as "a disease of the heart or blood vessels". The scope of the instant claims encompasses prevention (complete thwarting or warding off illness or total elimination or eradication of disease) or treatment of multiple complex disorders that may have unrelated manifestations including atherosclerosis, atherogenesis, coronary artery disease, heart valve disease, arrhythmia, heart failure, hypertension, orthostatic hypotension, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, cogenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiac sarcoma, cardiomyopathy, rheumatic heart diseases, restenosis, ischemic disease, pulmonary edema associated with acute myocardial infarction, thrombosis, platelet aggregation, platelet adhesion,

smooth muscle cell proliferation, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, atheroembolism and etc...(Harrisons' Principles Internal Medicine, 12th Edition, Chapter 198, pp. 835-1026; US 6656966).

The instant specification discloses the possible involvement of immunologic mechanism (e.g., immunoglobulins IgA, IgE and IgG) in pathogenesis of cardiovascular diseases; and the possible link between eosinophilia and cardiovascular mortality, particularly ischemic heart disease mortality and mortality from cerebrovascular disease (page 1, line 15 thru page 2, line 7). In the instant application, applicants show the activity of desloratadine in attenuating eosinophil chemotaxis, adhesion and superoxide generation in vitro study (Example) as the only working example. However, there is no demonstrated correlation that the tests and results apply to all of the diseases or disorders embraced by the instant claims. Especially, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to untility in humans or animals.

Since the significance of desloratadine in completely eliminating or preventing cardiovascular diseases or treating all of the diseases or disorders embraced by the instant claims cannot be predicted a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 10, 12-15 and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by (EP 0968715 A1).

The claims 10, 12-15 and 52 read on method of treating and/or preventing a cardiovascular disease characterized by platelet activating actor activity and/or superoxide generation in a human not suffering from an allergic and/or inflammatory condition of the skin or upper airway passages comprising administering an effective amount of desloratidine to said human. Further limitations include "the effective amount of desloratadine is in the range of about 2.5 mg/day to about 45 mg/day" (claim 12), "the effective amount of desloratadine is in the range of about 5 mg/day to about 15 mg/day" (claim 13), "the effective amount of desloratadine is in the range of about 5 mg/day to about 10 mg/day" (claim 14), "the effective amount of desloratadine is about 5 mg/day" (claim 15) and "atherosclerosis" (claim 52),

Buckland teaches the use of desloratadine (descarobethoxyloratadine) for the treatment of cardiovascular diseases such as arrhythmia (i.e., atrial fibrillation), wherein said desloratadine is administered in dosage range of about 0.1 mg/kg/day to about 100 mg/kg/day based on 70kg individual. See para. [0023], [0027], [0040] and claims 7-8.

Although the reference is silent about the claimed prophylactic use of descarboethoxyloratadine in preventing said cardiovascular characterized by platelet activating

factor activity and/or superoxide generation, namely atherosclerosis, in patient not suffering from an allergic and/or inflammatory condition of the skin or upper airway passages, such properties or characteristics must be inherently presented in the prior art method since the referenced method of administering the same compound such as desloratadine, in overlapping dosage amounts, to the same treatment groups (patient who is not suffering from an allergic and/or inflammatory condition of the skin or upper airway passages) inherently possessing the therapeutic effect for the same ultimate use as disclosed by the applicant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Applicant's attention is directed to Ex Parte Novitski 126 USPQ 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a haec verba recitation for such utility.

Response to Arguments

12. Applicant's arguments filed 07/28/06 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that there is sufficient guidance in the specification for the prophylactic utility of desloratidine in preventing said cardiovascular disease. Applicant asserts that the prevention of occurrence of said cardiovascular disease can be ascertained from the instant specification disclosing the activity of desloratidine in attenuating platelet activating factor activity as well as spontaneous superoxide generation in humans. To support the applicant argument, the applicant provides LI and Shah (Am J Physiol Regul Inter Comp Physol, 287, R1014-R1030, 2004) and Hospers et al. (Am J Epidemiol, 150(5):482-491,

1999). Applicant states that nexus between superoxide generation and cardiovascular disease is supported by the review article LI and Shah (Am J Physiol Regul Inter Comp Physol, 287, R1014-R1030, 2004) whereas the nexus between platelet activating factor activity and cardiovascular disease is supported by Hospers et al. (Am J Epidemiol, 150(5):482-491, 1999). Furthermore, the applicant asserts that the examiner's cited references ("NIH Heart Disease & Stroke Research: Fact Sheet", American Heart Association, 2004 and "Cardiovascular Disease Treatment for Stroke", Stanford Hospital and Clinics, 2003) also recognizes current research regarding treatment and prevention strategies for reducing the death rate from cardiovascular disease.

This argument is not found persuasive. Unlike the applicant's argument, there is no demonstrated correlation in the instant specification and the submitted documents that the tests and results apply to the prophylactic utility of using desloratadine in preventing or curing said cardiovascular diseases or disorders embraced by the instant claims.

In respect to the applicant's argument that there is the state of art recognition (the article cited by the Examiner) in "treatment and prevention strategies for reducing the death rate from cardiovascular disease", the examiner recognizes the current therapeutic approach (along with a purely symptomatic treatment) in treating cardiovascular disease or complication from cardiovascular disease or reducing the death rate resulted from the cardiovascular disease. However, the examiner does not recognize the instantly claimed prophylactic utility of desloratadine in preventing said cardiovascular disease. Contrary to the applicant's argument, two references cited by the examiner clearly recognizes no cure (prevention) for the cardiovascular disease despite of major advances in medical and surgical treatments (see last

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Amendment to the claims to remove new matter as set forth in this Office Action, absent other amendatory language, may necessitate reinstatement of previously made rejection(s) over prior art under 35 USC 102, 35 USC 103 and/or obvious type double rejection.

15. No Claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

paragraph of both articles, "But, despite major advances in the treatment of heart disease, stroke and other cardiovascular diseases, there is no cure for this country's No. 1 killer..." in American Heart Association, 2004 and "Although there is no cure for stoke, advances medical and surgical treatments are available, giving many stroke victims hope for optimum recovery" in Stanford Hospital and Clinics, 2003).

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to prevent the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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